Electron Transport Chain

Introduction

The electron transport chain is quite easy, apart from the details. What is most important is the setup. Grasp the setup, and the big reveal is quite simple to comprehend.

Let's start with the layers. There are two membranes, each a lipid bilayer, per mitochondrion. There is the outer layer, which contains the rest of the organelles and some space. Below the outer lipid bilayer but above the inner lipid bilayer is a fluid-filled compartment. These lipid bilayers have their hydrophilic heads facing out, and their **hydrophobic lipophilic tails pointing inward**. To get through these lipid bilayers, a molecule needs to be unionized, nonpolar, and lipophilic—charged, polar ions such as H^+ do not cross easily. This will become important in the discussion of building an electrochemical gradient.

Glycolysis occurs in the **cytoplasm**, outside the mitochondrion. In the presence of oxygen, pyruvate goes into the mitochondrion and becomes acetyl-CoA. **Pyruvate dehydrogenase** (PDH) and the **citric acid cycle** (TCA) both occur **inside the mitochondrion**, within the **inner layer**. The NADH and $FADH_2$ produced by these reactions are immediately available to the electron transport chain. The NADH made in the cytoplasm finds it way to the mitochondrial matrix via the malate shuttle (NADH comes over intact) or through the α-glycerol-phosphate-shuttle (NADH gets "downgraded" to $FADH_2$). Those shuttles' names were not bolded. That was intentional.

The **mitochondrial matrix**, the "**inside**" of the mitochondrion, is where the **action is**. The matrix is where $FADH_2$ and NADH are made by PDH and TCA. The matrix side of the inner membrane is where all the complexes that make up the ETC are located, and where they interact with NADH and $FADH_2$. This is where the final product, F_OF_1-ATP-synthase, energizes ADP to ATP. The matrix is where ATP is made.

Between the outer and inner membrane is the **intermembrane space**. This is where all the **power is**. Because the inner and outer mitochondrial membranes are lipid bilayers, any ions placed in this space are stuck there. This allows both an electrical gradient (pumping positive charges into the space makes the matrix relatively negative, favoring the return of that positive charge into the matrix) and a chemical gradient (pumping an ion against its concentration gradient favors the return of that ion back into the matrix). The mitochondrion is set up to **pump out H^+ into the intermembrane space** at many places. It allows the H^+ back into the matrix at discrete locations.

The **F_OF_1-ATP-synthase** makes **ATP**. It is the **only place** H^+ is allowed back into the matrix from the intermembrane space. As the H^+ ion comes back through the F_O portion—the channel—the energy released is harnessed by the F_1 portion, spinning like a water wheel, generating physical force that enables the F_1 portion to build **ADP into ATP**.

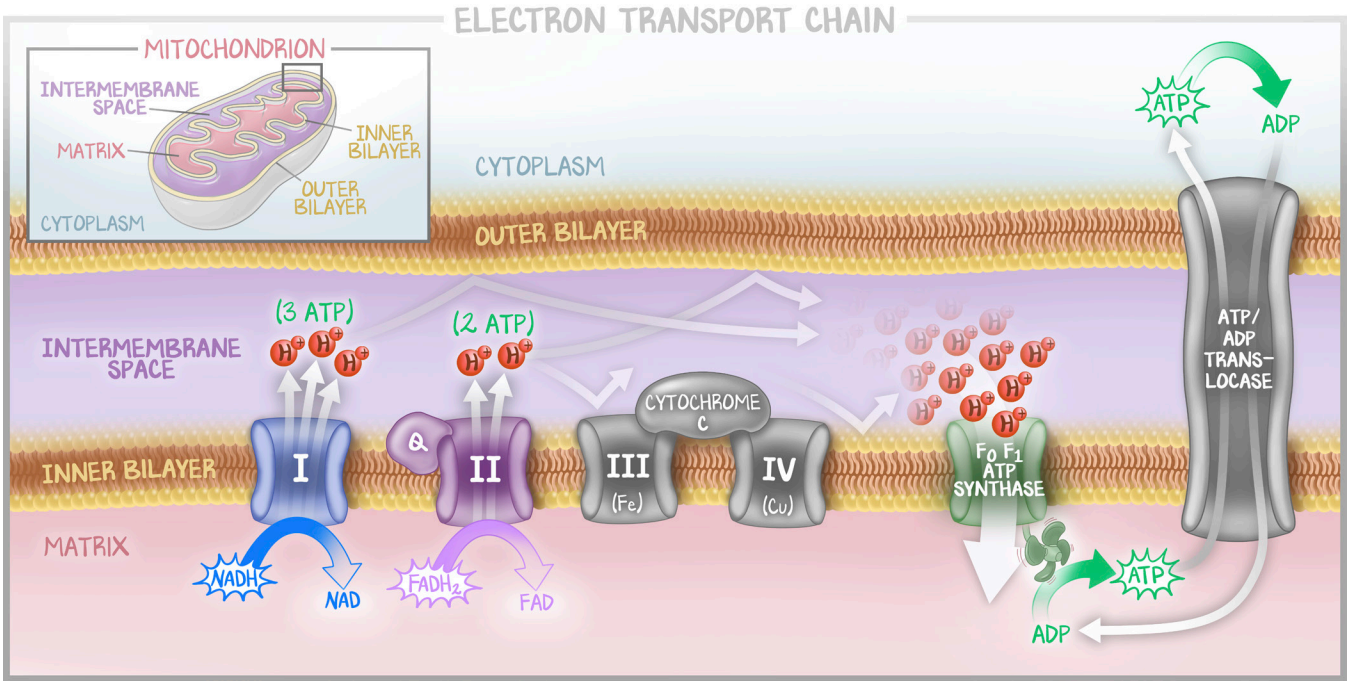

Figure 6.1: ETC Steps
The key energy transfers in the ETC, along with location.

Everything that is the electron transport chain happens in the mitochondrion. Almost all the substrate for the electron transport chain is made in the mitochondrion (those two NADHs from glycolysis are the only ones that aren't made in the mitochondrion). Every step. Every complex. Every cycle or pathway we have talked about so far in metabolism has been to establish a proton-ion gradient so that the F_OF_1-ATP-synthase can spin one time, for one hydrogen, to make one ATP.

The Truth about Electron Flow

The truth is that electrons flow from complex I through the cytochrome Q-complex II, down complex III, into cytochrome *c*, and through complex IV until they finally reach oxygen. Oxygen is there to receive the electron. H^+ ions are pumped across the inner membrane at complex I, III, and IV. This doesn't make for a pretty image. It also doesn't really help explain what's happening. The takeaway from these facts is that, because NADH interacts with complex I, a total of three hydrogen ions are pumped across per NADH (I, III, IV), which correspond to three ATP generated per NADH and two hydrogen ions pumped across per $FADH_2$ (III, IV), which correspond to two ATP per $FADH_2$. Beyond that, the accuracy of "following the electron flow" just confuses people who aren't biochemists or physics majors. We will come back to this truth in Metabolism #7: *Electron Transport Chain Pharmacology*, but for every other evaluation of this system, the following model works.

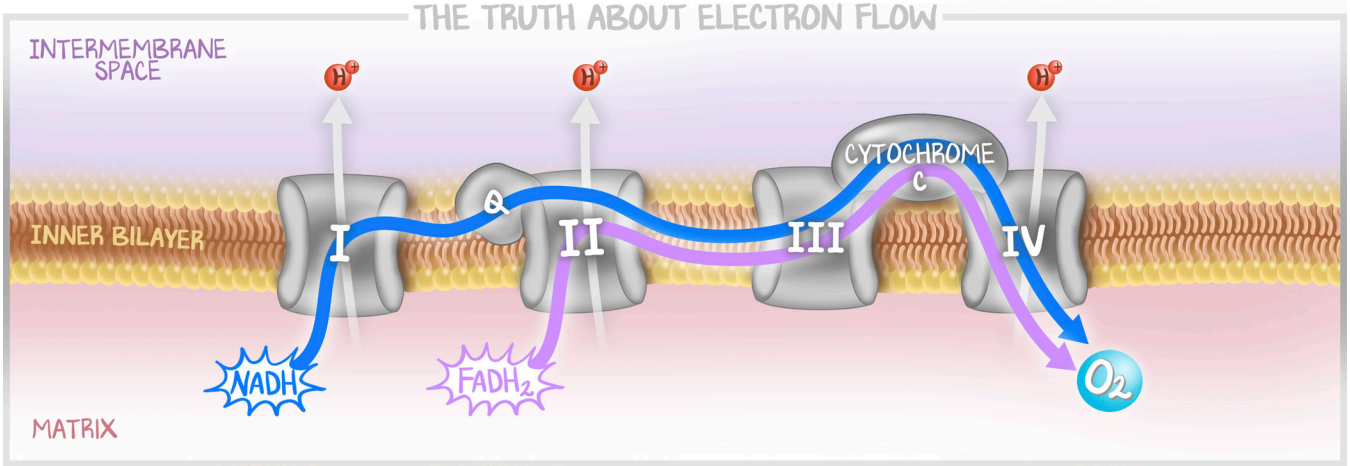

Figure 6.2: The Truth about Electron Flow
Electrons are the transferred-to complexes, and those electrons flow through the complexes until they reach oxygen at complex IV. This level of detail was needed for undergraduate biochemistry, but affords no useful information for medical biochemistry.

The Model We Use

Complex I is for **NADH**. For every NADH molecule that binds to complex I, complex I sends out **3 H^+ into the intermembrane space**, and regenerates the NAD molecule to go back to the TCA cycle or PDH.

Complex II is for $FADH_2$. For every $FADH_2$ molecule that binds to complex II, complex II sends out **2 H^+ into the intermembrane space**, and regenerates the FAD molecule to go back to the TCA cycle.

Complex III *(b/c1)* and **cytochrome *c*** have **iron in them**. Iron is in the heme group. This matters a lot when you say words like oxidize, reduce, and flow of electrons. "Complex-III-iron" is much easier to remember.

Complex IV *(a/a3)* has **copper (Cu)** in it. It's unique because copper is rarely found in heme groups. This matters more with words like oxidize, reduce, and flow of electrons. "Complex-4-copper" is much easier to remember.

F_OF_1 ATP synthase makes ATP. One H^+ is worth one ATP. The F_O portion lets the H^+ back through; the F_1 portion is the waterwheel that generates the force needed for ADP to go to ATP.

Therefore, since the synthase is the only place for H^+ to come back through the inner membrane, and one H^+ is worth one ATP, every **NADH** (3 H^+ at complex I) yields **3 ATP**, and every **$FADH_2$** (2 H^+ at complex II) yields **2 ATP**.

Without oxygen this doesn't happen. The process by which oxygen is used and ATP synthase makes oxygen is called **oxidative phosphorylation** (oxidative, O_2; phosphorylation, ADP to ATP, adenine-PP to adenine-PPP).

The Energy Count

The net of +4 ATP made by substrate-level phosphorylation (substrate-level is not oxidative) keep their count of 4.

Net +10 NADH, at 3 ATP each, yield 30 ATP.
Net +2 $FADH_2$, at 2 ATP each, yield 4 ATP.

Add them all together and one glucose molecule generates a **net of 38 ATP**. Be careful, because we deducted the two energizing steps at the very beginning of glycolysis (hexokinase and PFK-1). Therefore, the **gross ATP made is 40**. All along in this metabolism course, the net count has been our default. Every glucose molecule **starts by spending 2 ATP**, then the entire process **makes 40 ATP** leaving a **net of 38**. Output 40, input 2, net 38. This repetition is on purpose.

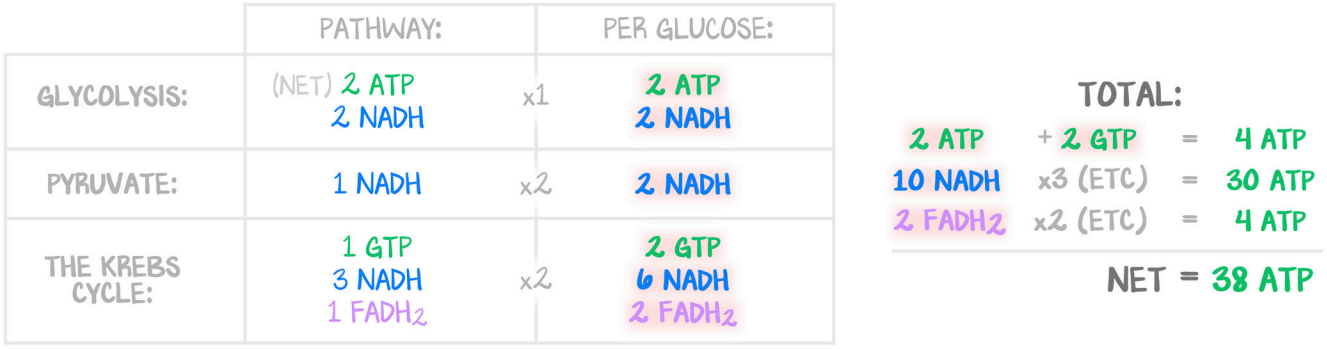

Figure 6.3: ATP Energy Creation Calculation
The net of +4 ATP came from −2 ATP during glycolysis, followed by +4 ATP during glycolysis, and +2 GTP from the TCA. So the NET is +4.

Hypoxemia

We learned that in **anaerobic conditions** pyruvate is converted to lactate. Lactate regenerates the NAD needed for more glycolysis. In the absence of oxygen, every glucose molecule yields a net ATP of two. Two is not 38. Anaerobic metabolism is about 5% as efficient as aerobic metabolism. If a cell is maintained by, say, an Na-K-ATPase, which is heavily reliant on ATP to work, and **it loses 95% of its ATP**, guess what happens? Yeah, nothing good. The membrane potential is lost, entropy wins, the cell swells and dies. Before it goes, though, it will try to live, burn glucose to lactate…and lactate will build up—the last-ditch effort to get some ATP. The tissues at highest risk are those that are the most metabolically active—**brain**, **heart**, and **kidneys**. The accumulation of lactate (osmotic) and the loss of membrane potential causes the cells to die (undergo necrosis). This leads to obvious dysfunction.

It is unsurprising that we can **measure lactic acid** (lactate) levels in the blood. Elevated lactic acid means anaerobic metabolism, and we assume clinically, that anaerobic metabolism in humans means poor tissue perfusion. Which tissue is poorly perfused, and for what reason, is NOT demonstrated by an elevated lactate.

Likewise, **lactate dehydrogenase** (LDH) is used as a marker for inflammation—excess activity of cells. It is far less specific and can be elevated in hemolysis (red cells have no mitochondria) or in any inflammatory reaction (the local tissue or the immune system is ramping up activity, demanding more oxygen).

When **heart cells die** they release **heart-specific enzymes** called **troponin I**. The troponins are released because the cells die, lyse, and myocyte parts go everywhere. LDH and lactic acid elevate because of

hypoxia in the tissues and the loss of oxidative phosphorylation. Don't be tricked—lactate is for poor perfusion (shock of any kind), LDH is any inflammation, and troponin is myocyte death. What does this have to do with ETC? The answer is that while these labs are quite separated in clinical medicine, the test leverages students' lack of clinical experience and adds potential pitfalls in the form of a wealth of biochemical pathways.

Mitochondrial Mutations

If you're going for a 290, look elsewhere. We're actively warning you away from learning mutations of the ETC.